Journal of Cardiology 60 (2012) 508–513

Contents lists available at SciVerse ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Usefulness of cardiac biomarkers in the prediction of right ventricular dysfunction before echocardiography in acute pulmonary embolism

Hong Sang Choi (MD), Kye Hun Kim (MD)*, Hyun Ju Yoon (MD), Young Joon Hong (MD), Ju Han Kim (MD), Youngkeun Ahn (MD), Myung Ho Jeong (MD), Jeong Gwan Cho (MD), Jong Chun Park (MD), Jung Chaee Kang (MD)

The Heart Center of Chonnam National University Hospital, The Research Institute of Medical Sciences of Chonnam National University, Gwangju, Republic of Korea

ARTICLE INFO

Article history:
Received 20 December 2011
Received in revised form 27 June 2012
Accepted 30 June 2012
Available online 17 August 2012

Keywords:
Biomarker
Ventricular dysfunction
Pulmonary embolism

ABSTRACT

Background: The aim of this study was to investigate a useful cardiac biomarker for predicting echocardiographic right ventricular (RV) dysfunction in patients with acute pulmonary embolism (APE).
Methods: A total of 84 patients with APE were divided into two groups: patients with RV dysfunction (group I, $n = 51$, 61.8 ± 15.1 years) versus without RV dysfunction (group II, $n = 33$, 66.8 ± 13.6 years). Cardiac biomarkers were compared between the groups.
Results: The level of N-terminal pro-brain-type natriuretic peptide (NT-proBNP), cardiac specific troponin T (cTnt), and I (cTni) was significantly elevated in group I compared to group II, but the level of creatine kinase and high-sensitivity C-reactive protein was not different. By receiver operating characteristic curve analysis, the area under the curve to predict RV dysfunction was 0.912 for NT-proBNP, 0.797 for cTnt, and 0.766 for cTni. The optimal cut-off value to predict RV dysfunction was 620.0 pg/mL for NT-proBNP (sensitivity: 90.2%, specificity: 75.8%), 0.016 ng/mL for cTnt (sensitivity: 82.4%, specificity: 78.8%), and 0.055 ng/mL for cTni (sensitivity: 86.3%, specificity: 66.7%). NT-proBNP > 620 pg/mL and cTnt > 0.016 ng/mL were independent predictors of RV dysfunction on multivariate analysis after adjustment for the baseline characteristics.
Conclusions: NT-proBNP, cTnt, and cTni were significant serologic predictors of RV dysfunction in APE. Measurements of NT-proBNP, cTnt, and cTni are simple and useful in the risk stratification or treatment of APE.

Introduction

Acute pulmonary embolism (APE) is not uncommon in clinical practice, and the mortality of APE is still high despite advances in diagnostic modalities and therapeutic options [1–3]. It has been proved that patients with massive APE, defined by systemic hypotension, should be treated with thrombolysis or embolectomy [4,5].

Right ventricular (RV) dysfunction is a well-known predictor of early death, and thus early identification of RV dysfunction is critical in the risk stratification or management of APE [6–10]. Transthoracic echocardiography (TTE) has been used as a method of choice to identify the patients with RV dysfunction [11]. Cardiac biomarkers such as troponin and N-terminal pro-brain-type natriuretic peptide (NT-proBNP) are known to be useful not only in the diagnosis, but also in the risk stratification of various cardiac diseases [12,13]. Furthermore, recent studies have suggested that cardiac biomarkers are associated with an increased risk of mortality in patients with APE, even in hemodynamically stable patients [14–18], and thus cardiac biomarkers are useful in the risk stratification of APE. It has been suggested that cardiac biomarkers are associated with the presence of RV dysfunction on echocardiography. Although several studies have been conducted to prove the relationship between cardiac biomarkers and RV dysfunction on echocardiography [19–23,10,24], the comparisons among cardiac biomarkers in the prediction of RV dysfunction and the optimal cutoff values of cardiac biomarkers to predict RV dysfunction were poorly evaluated.

Therefore, the aim of the present study was to investigate the most useful serologic predictors of RV dysfunction and to investigate the optimal cutoff values of cardiac biomarkers to predict RV dysfunction in patients with APE.

* Corresponding author at: The Heart Center of Chonnam National University Hospital, 42 Jebong-ro, Dong-gu, Gwangju 501-757, Republic of Korea.
Tel.: +82 62 220 6978; fax: +82 62 223 3105.
E-mail address: christiankyehun@hanmail.net (K.H. Kim).

0914-5087/$ – see front matter © 2012 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jjcc.2012.07.006

Materials and methods

Study design and population

The present study was a single center retrospective observational study, and the study protocol was approved by the Institutional Review Board of Chonnam National University Hospital.

The diagnosis of APE was confirmed by the presence of filling defects within the pulmonary arterial systems on helical computed tomographic pulmonary angiography (CTPA) in patients who presented with dyspnea, tachycardia, chest discomfort, or hemoptysis. From 2004 to 2007, a total of 101 consecutive patients with APE were included initially. Of these, 17 patients were excluded from the study; nine patients with lack of biomarker tests; 3 patients with combined left heart failure; 2 patients with known cor pulmonale; 2 patients without initial echocardiogram; 1 patient with end-stage renal disease. The remaining 84 patients with APE were enrolled finally in the present study, and they were divided into two groups based on the presence of RV dysfunction on echocardiography: patients with RV dysfunction (group I, $n = 51$, 61.8 ± 15.1 years, 31 females) versus patients without RV dysfunction (group II, $n = 33$, 66.8 ± 13.6 years, 20 females). Obesity was defined as body-mass index > 27 kg/m^2, and immobilization as prolonged bed rest associated with orthopedic surgery, major fracture, or cerebrovascular accidents, or prolonged sitting during travel. The thrombophilic condition was defined as the patients with known risk factors for venous thrombosis such as factor V leiden, protein C or S deficiency, anti-phospholipid syndrome, or essential thrombocytosis.

TTE examination

TTE was performed within 6 h after diagnosis of APE by CTPA for the risk stratification or clinical decision-making of therapeutic strategy.

The presence of RV dysfunction was confirmed only based on the echocardiographic findings in the present study. The demonstration of RV free wall hypokinesia or akinesia on echocardiographic examination was considered as the definite diagnosis of RV dysfunction in patients with APE. RV enlargement, defined by the ratio of RV to LV size more than 1 in apical 4 chamber view without obvious causes, accompanied by pulmonary hypertension in patients with APE was also considered as RV dysfunction in the present study [11]. Fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and RV systolic pressure were also measured as the additional parameters of RV function according to the current guideline of the American Society of Echocardiography [25]. Eccentricity index (EI) which reflected the degree of RV pressure overload was measured at the parasternal short-axis view during both end-systole and end-diastole. EI was calculated by measuring the ratio D2/D1, where D1 is the antero-posterior dimension and D2 is the transverse dimension of the left ventricle.

Measurement of cardiac biomarkers

NT-proBNP, cardiac specific troponin T (cTnt), I (cTni), creatine kinase (CK), and MB fraction of CK (CK-MB), and high-sensitivity C-reactive protein (hsCRP) were measured as cardiac biomarkers within 1 h after the diagnosis of APE and before the initiation of thrombolytic therapy.

Serum NT-proBNP was measured using an electrochemiluminescence sandwich immunoassay method for NT-proBNP with an Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland). This method has high sensitivity and specificity, and large detection range. The analytic range of the NT-proBNP assay extends from 5 to 35,000 pg/mL. The reference value varies according to age and gender, and <88 pg/mL for men and <153 pg/mL for women in our institution. cTnt was measured using electrochemiluminescence sandwich immunoassay method with an Cobas e 411 (Roche Diagnostics), and the reference range for cTnt was <0.1 ng/mL. cTni was also measured using one step Enzyme Immunoassay with a Dimension RxL Max (Siemens, Munich, Germany), and the reference range for cTni was <0.05 ng/mL. And hsCRP was measured by the immunoturbidimetric CRP-Latex (II) high-sensitivity assay using an Olympus 5431 autoanalyzer with reference range of <0.5 mg/dL.

Table 1
Baseline clinical characteristics.

	Group I ($n = 51$)	Group II ($n = 33$)	p-Value
Age (years)	61.8 ± 15.1	66.8 ± 13.6	0.128
Females (%)	31 (60.8)	20 (60.6)	0.987
SBP (mmHg)	113.1 ± 19.8	135.2 ± 16.7	<0.001
DBP (mmHg)	72.7 ± 13.7	82.5 ± 10.5	<0.001
Heart rate (beat/min)	88.1 ± 13.9	81.7 ± 10.6	0.028
Clinical symptoms			
Dyspnea (NYHA class)	2.8 ± 1.0	1.9 ± 0.9	<0.001
Chest pain (%)	21 (41.2)	12 (36.4)	0.659
Hemoptysis (%)	2 (3.9)	6 (18.2)	0.069
Syncope (%)	10 (19.6)	4 (12.1)	0.369
Cyanosis (%)	5 (9.8)	0 (0.0)	0.064
Predisposing conditions			
Previous DVT or PTE (%)	6 (11.8)	5 (15.2)	0.653
Immobilization (%)	7 (13.7)	5 (15.2)	0.855
Smoking (%)	10 (19.6)	12 (36.4)	0.088
Obesity (%)	12 (23.5)	7 (21.2)	0.804
Malignancy (%)	6 (12.2)	4 (12.1)	0.961
Thrombophilic condition (%)	1 (2.0)	1 (3.0)	0.754
Pregnancy (%)	1 (2.0)	0 (0.0)	0.418

SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism.

Statistical analysis

The Statistical Package for Social Sciences for Windows (version 17.0, Chicago, IL, USA) was used for statistical analyses. Data were expressed as mean ± standard deviation for continuous variables and percentage for categorical data.

Chi-square test was used to compare differences in categorical values between the two groups. Independent t-test was used to compare differences in continuous variables. Receiver operating characteristic (ROC) curve analysis was conducted to identify the optimal cut-off value of biomarkers to predict RV dysfunction. Correlation analysis between cardiac biomarkers and the parameters of RV dysfunction was established by the Pearson correlation. To identify the independent biochemical predictors of RV dysfunction, multivariate logistic regression analysis adjusted by the baseline clinical characteristics including age, sex, blood pressure, heart rate, and creatinine level was applied to the significant cardiac biomarkers associated with RV dysfunction. A p-value less than 0.05 was considered as statistically significant.

Results

Baseline clinical characteristics

Baseline clinical characteristics are summarized in Table 1. Age, sex, and the predisposing conditions were not different between the groups. Systolic and diastolic blood pressures were significantly lower, and the heart rate was significantly higher in group I than in group II. The degree of dyspnea was significantly more severe in group I than in group II.

Table 2
Echocardiographic findings of the patients.

	Group I (n = 51)	Group II (n = 33)	p-Value
LVEDD (mm)	40.5 ± 6.4	46.4 ± 5.1	<0.001
LVESD (mm)	26.6 ± 5.2	30.1 ± 4.9	0.003
LVEF (%)	63.8 ± 8.5	64.6 ± 6.9	0.638
E (m/s)	0.53 ± 0.12	0.65 ± 0.17	0.001
A (m/s)	0.77 ± 0.10	0.82 ± 0.13	0.046
DT (s)	190.5 ± 32.6	230.2 ± 78.5	0.002
Em (m/s)	6.0 ± 1.0	6.4 ± 1.2	0.156
E/Em	8.9 ± 2.2	10.8 ± 3.6	0.004
LA dimension (mm)	31.7 ± 6.2	35.4 ± 4.7	0.004
RVSP (mmHg)	55.7 ± 10.6	42.9 ± 10.2	<0.001
RVEDD/LVEDD	0.88 ± 0.21	0.61 ± 0.11	<0.001
RV FAC (%)	27.8 ± 11.6	53.4 ± 13.1	<0.001
TAPSE (mm)	11.4 ± 4.4	16.4 ± 4.4	<0.001
EI (diastolic)	1.27 ± 0.21	1.01 ± 0.08	<0.001
EI (systolic)	1.35 ± 0.31	1.07 ± 0.07	<0.001

LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; *E*, early diastolic velocity of mitral inflow; *A*, late diastolic velocity of mitral inflow; DT, deceleration time of mitral inflow; Em, early diastolic velocity of septal mitral annulus; LA, left atrium; RVSP, right ventricular systolic pressure; RVEDD, right ventricular end-diastolic dimension; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; EI, eccentricity index.

TTE findings

Baseline TTE findings are summarized in Table 2. LV and left atrial chamber sizes were significantly smaller, and RV systolic pressure was significantly greater in group I than in group II. Early (*E*) and late diastolic velocities (*A*) of mitral inflow and early diastolic septal annular velocity (Em) were significantly lower, and deceleration time of mitral inflow was significantly shorter in group I than in group II. The indices of RV dysfunction were more significantly impaired in group I than in group II.

Cardiac biomarkers and RV dysfunction

The results of cardiac biomarkers are summarized in Table 3. The levels of NT-proBNP and cardiac troponins were significantly elevated in group I compared to group II. However, the levels of hsCRP and CK were not different between the groups.

By ROC curve analysis, the area under the curve to predict RV dysfunction on echocardiography was 0.912 for NT-proBNP, 0.797 for cTnt, and 0.766 for cTni. The optimal cut-off value to predict RV dysfunction was 620.0 pg/mL for NT-proBNP (sensitivity: 90.2%, specificity: 75.8%), 0.016 ng/mL for cTnt (sensitivity: 82.4%, specificity: 78.8%), and 0.055 ng/mL for cTni (sensitivity: 86.3%, specificity: 66.7%) (Fig. 1).

Correlation between cardiac biomarkers and the parameters of RV dysfunction was measured by Pearson correlation and summarized in Table 4. NT-pro-BNP, cTnt, and cTni showed significant positive correlation with RVEDD/LVEDD ratio, systolic and diastolic EI, and SPAP. NT-pro-BNP, cTnt, and cTni showed significant negative correlation with TAPSE.

Table 3
Cardiac biomarkers and right ventricular dysfunction.

	Group I (n = 51)	Group II (n = 33)	p-Value
NT-proBNP (pg/mL)	4079.8 ± 3127.9	638.1 ± 759.9	<0.001
cTnt (ng/mL)	0.20 ± 0.30	0.05 ± 0.11	0.002
cTni (ng/mL)	0.77 ± 1.48	0.21 ± 0.47	0.015
hsCRP (mg/dL)	3.1 ± 3.3	2.5 ± 3.2	0.364
CK (U/L)	119.5 ± 84.5	117.1 ± 99.6	0.905
CK-MB (U/L)	8.7 ± 4.4	8.0 ± 5.1	0.494

NT-proBNP, N-terminal-pro-B-type natriuretic peptide; cTnt, cardiac specific troponin T; cTni, cardiac specific troponin I; hsCRP, high-sensitivity C-reactive protein; CK, creatine kinase; CK-MB, MB fraction of CK.

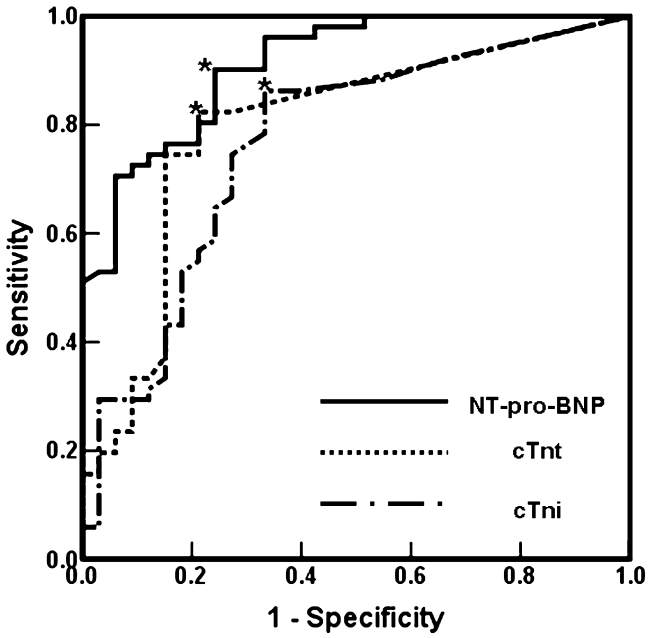

Fig. 1. Receiver operating characteristic curve analysis to predict right ventricular dysfunction on echocardiography. Asterisks indicate the optimal cut-off point of each variable. NT-proBNP, N-terminal-pro-B-type natriuretic peptide; cTnt, cardiac specific troponin T; cTni, cardiac specific troponin I.

Table 4
Correlation between cardiac biomarkers and the echocardiographic indices of right ventricular dysfunction.

Variables	NT-proBNP	cTnt	CTni
RVEDD/LVEDD ratio	0.651**	0.528**	0.469**
EI (systolic)	0.709**	0.658**	0.600**
EI (diastolic)	0.668**	0.548**	0.493**
TAPSE	−0.440**	−0.326*	−0.220*
FAC	−0.655**	−0.406**	−0.332**
SPAP	0.634**	0.364**	0.180

NT-proBNP, N-terminal-pro-B-type natriuretic peptide; cTnt, cardiac specific troponin T; cTni, cardiac specific troponin I; RVEDD, right ventricular end-diastolic dimension; LVEDD, left ventricular end-diastolic dimension; EI, eccentricity index; TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change; SPAP, systolic pulmonary artery pressure.
* Numeric values represent the Pearson correlation coefficient: $p < 0.05$.
** Numeric values represent the Pearson correlation coefficient: $p < 0.01$.

Multivariate logistic regression analysis was performed to identify the independent biochemical predictors of RV dysfunction. NT-proBNP > 620 pg/mL, cTnt > 0.016 ng/mL, and age were significant independent predictors of RV dysfunction after the adjustment for the baseline clinical characteristics (Table 5).

Table 5
Predictors of echocardiographic right ventricular dysfunction by multivariate logistic regression analysis.

Variable	Odds ratio	95% CI	p-Value
NT-proBNP > 620 pg/mL	5.038	2.352–9.598	<0.001
cTnt > 0.016 ng/mL	5.582	3.786–8.232	0.003
cTni > 0.055 ng/mL	1.403	0.109–18.182	0.796
Age	1.080	1.020–1.144	0.009
Serum creatinine level	1.349	0.223–8.130	0.744
Female	0.939	0.171–5.157	0.942

CI, confidence interval; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; cTnt, cardiac specific troponin T; cTni, cardiac specific troponin I.

Table 6
Cardiac biomarkers and in-hospital mortality.

	No death (n = 78)	Death (n = 6)	p-Value
NT-proBNP (pg/mL)	2425.2 ± 2818.6	6660.2 ± 2582.7	0.001
cTnt (ng/mL)	0.13 ± 0.25	0.34 ± 0.24	0.049
cTni (ng/mL)	0.54 ± 1.26	0.77 ± 0.29	0.649
hsCRP (mg/dL)	2.8 ± 3.3	3.5 ± 2.8	0.607
CK (U/L)	114.8 ± 91.7	167.8 ± 47.4	0.166
CK-MB (U/L)	8.3 ± 4.8	9.7 ± 1.8	0.486

NT-proBNP, N-terminal-pro-B-type natriuretic peptide; cTnt, cardiac specific troponin T; cTni, cardiac specific troponin I; hsCRP, high sensitivity C-reactive protein; CK, creatine kinase; CK-MB, MB fraction of CK.

In-hospital mortality

Six patients (7.1%) died due to the consequences of APE during hospitalization. The mortality rate was significantly higher in group I than in group II (11.8% versus 0.0%, $p = 0.041$).

The levels of NT-proBNP and cTnt were significantly associated with in-hospital mortality in patients with APE, but the levels of cTni, CK, and hsCRP were not associated with in-hospital mortality (Table 6).

By ROC curve analysis, the area under the curve to predict in-hospital mortality was 0.870 for NT-proBNP and 0.865 for cTnt. The optimal cut-off value to predict in-hospital mortality was 2664.0 pg/mL for NT-proBNP (sensitivity: 100.0%, specificity: 66.7%), 0.09 ng/mL for cTnt (sensitivity: 100.0%, specificity: 76.9%) (Fig. 2).

Discussion

The present study comprehensively evaluated and compared the roles of commonly used cardiac biomarkers in the risk stratification or evaluation of APE. The main finding of the present study was that the levels of NT-proBNP and cardiac troponins were significant predictors of echocardiographic RV dysfunction, and the level of NT-proBNP and cTnt could predict in-hospital mortality in patients with APE. The NT-proBNP showed best sensitivity and specificity to predict echocardiographic RV dysfunction, and cTnt showed best sensitivity and specificity to predict in-hospital mortality in patients with APE. In addition, the present study also suggested the optimal cutoff value of NT-proBNP and cardiac troponins to predict echocardiographic RV dysfunction or in-hospital death. Based on the results of the present study, it is expected that simple measurements of cardiac biomarkers would be useful to predict the presence of RV dysfunction, especially in hospitals where the echocardiographic examinations or experts in echocardiography are not readily available.

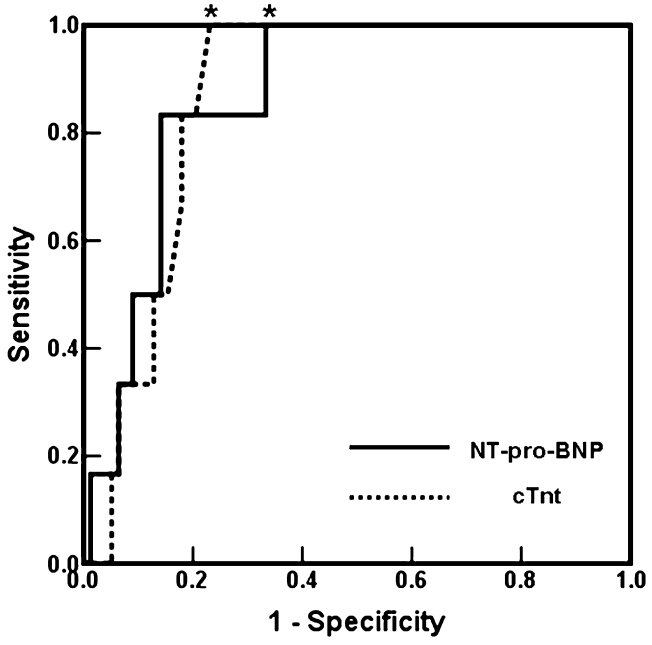

Fig. 2. Receiver operating characteristic curve analysis to predict in-hospital mortality. Asterisks indicate the optimal cut-off point of each variable. NT-proBNP, N-terminal-pro-B-type natriuretic peptide; cTnt, cardiac specific troponin T.

RV dysfunction on echocardiography is an independent and useful predictor of mortality in patients with APE, regardless of hemodynamic status [1]. Thus, the early identification of RV dysfunction is critical in the clinical decision-making of therapeutic strategy in patients with APE. Echocardiography has been the most accepted method for the detection of RV dysfunction. However, there are some limitations in the routine clinical use of echocardiography in patients with APE. Because the results of echocardiography largely depend on the experience of the operator, an expert in echocardiography would be essential to identify the patients with RV dysfunction accurately. Furthermore, echocardiography is not always readily available, especially in private clinics or secondary hospitals or at nighttime. In contrast to echocardiographic examination, cardiac biomarkers can be readily available in all patients at any time without operator-dependent variability. Therefore, the measurement of cardiac biomarkers would be a simple and useful method as an alternative to echocardiography.

NT-proBNP is a 76-amino acid N-terminal fragment of proBNP and released 1:1 fashion with BNP. It is released from ventricular cardiac myocytes in response to ventricular volume or pressure overload [17]. Because RV dysfunction is usually accompanied by RV volume or pressure overload, BNP or NT-proBNP could be a useful biomarker of RV dysfunction if there are no other reasons for BNP elevation, such as left heart failure or renal failure. In the present study, the level of NT-proBNP showed good sensitivity and specificity to predict RV dysfunction and in-hospital mortality in patients with APE, regardless of hemodynamic status. Some of the previous studies also demonstrated the association between the level of BNP and echocardiographic RV dysfunction and suggested the optimal cutoff values to predict RV dysfunction. Krüger et al. [19] suggested that a BNP > 90 pg/mL could predict RV dysfunction, but the sensitivity was relatively low (64%) despite the reasonable specificity (94%). Furthermore, BNP level was not a predictor of in-hospital complications and mortality in their study. In the study of Yardan et al. [22], however, the level of BNP could predict the presence of RV dysfunction with better sensitivity (93.8%) and specificity (91.7%), even though they used the same optimal cut-off value of BNP (>90 pg/mL). Pieralli et al. [23] also reported similar results that the level of BNP could predict RV dysfunction with good sensitivity (86%) and specificity (100%), and the level of BNP was also a predictor of in-hospital complications. The clinical significance of NT-proBNP to predict RV dysfunction or prognosis in patients with APE has been proved to be similar to those of BNP [10,24]. However, the optimal cutoff value for NT-proBNP to predict RV dysfunction or mortality is poorly evaluated, and thus the authors want to evaluate the optimal cutoff value of NT-proBNP to predict RV dysfunction. In the present study, the level of NT-proBNP > 620 pg/mL could predict the presence of RV dysfunction with relatively acceptable sensitivity (90.2%) and specificity (75.8%) to use in clinical practice, and the level of NT-proBNP also could predict in-hospital mortality in patients with APE.

Cardiac-specific troponins, cTnt and cTni, are reliable markers of myocardial injury and known to be associated with RV dysfunction or outcomes [26–28], but the optimal cut-off values for predicting RV dysfunction were poorly evaluated. The present

study suggested the optimal cut-off value to predict RV dysfunction or in-hospital mortality in patients with APE. According to the results of the present study, among cardiac biomarkers, both cTnt and NT-proBNP were useful markers of in-hospital mortality, but cTni was not a predictor of in-hospital mortality even though the absolute value of cTni was higher in the dead than in the survivors. The reason why cTnt may predict in-hospital death, but not cTni is unclear. Considering the difference in the absolute value of cTni between the dead and the survivors, the small number of the study population would be one possible explanation. cTnt was not measured by the highly sensitive method, but by the conventional method in the present study. However, recent studies have suggested that the measurement of highly sensitive cTnt would be a more sensitive and specific method for diagnosing acute coronary syndrome than the conventional method [29], and highly sensitive cTnt correlated with ventricular hypertrophy in patients with essential hypertension [30] and cardiac dysfunction evaluated by echocardiography and natriuretic peptide in patients with heart failure [31]. To clarify the association between highly sensitive cTnt and echocardiographic parameters of RV dysfunction in patients with APE, further studies should be conducted in the near future.

The role of other cardiac biomarkers, such as CRP or CK-MB, in APE was evaluated in some studies. CRP is a well known biomarker for cardiovascular disease or events in various clinical settings [32,33], but the role of CRP in the prediction of RV dysfunction or mortality in APE was poorly evaluated. The recent study of Abul et al. suggested that CRP would be a predictor of mortality in patients with APE [34]. However, the results of the present study suggested that CRP was not a predictor of RV dysfunction or mortality in patients with APE. Therefore, a larger randomized clinical study will be needed in the future to elucidate the role of CRP in APE. Although a few studies suggested that CK-MB was a predictor of RV dysfunction [35] or mortality [36], CK-MB was neither a predictor of RV dysfunction nor mortality of APE in the present study.

Although the LV systolic function as measured by EF was not different, the parameters of diastolic function were significantly different between the groups. *E*, *A*, Em, and *E*/Em were significantly lower in patients with RV dysfunction than without RV dysfunction. The reason for the lower *E* velocity in patients with RV dysfunction might be explained by the fact that the decreased RV function and thrombi within pulmonary vasculatures may induce LV preload reduction. The decreased RV wall motion may induce decreased septal wall motion and thus Em would become lower in patients with RV dysfunction than without RV dysfunction. *E*/Em was significantly lower in patients with RV dysfunction than without RV dysfunction in the present study. From this observation, it is suggested that the LV preload might be more severely affected by RV dysfunction than the septal wall motion.

The present study has several potential limitations. First, the present study is not a randomized controlled prospective study, and thus has all the limitations of a retrospective study. Second, although the blood samples for cardiac biomarkers were taken as soon as possible after the diagnosis of APE, the timing of blood samplings might differ among the patients. Third, seventeen patients with APE were excluded from the present study for this and other reasons, and thus the results of the present study may not reflect all characteristics of APE.

In conclusion, the results of the present study demonstrated that NT-proBNP and cardiac troponins were significant predictors of echocardiographic RV dysfunction in patients with APE. The levels of cTnt and NT-proBNP were also significant predictors of in-hospital mortality. Therefore, the simple measurements of these cardiac biomarkers would be helpful in clinical decision-making or risk stratification in patients with APE, especially in the clinics where echocardiographic examinations or the experts in echocardiography were not readily available.

References

[1] Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386–9.

[2] Heit JA, Melton 3rd LJ, Lohse CM, Petterson TM, Silverstein MD, Mohr DN, O'Fallon WM. Incidence of venous thromboembolism in hospitalized patients vs community residents. Mayo Clin Proc 2001;76:1102–10.

[3] Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser KD, Rauber K, Iversen S, Redecker M, Kienast J. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997;30:1165–71.

[4] Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:401S–28S.

[5] Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP, Vahanian A, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008;29:2276–315.

[6] Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, Conti A, Agnelli G, Berni G. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000;101:2817–22.

[7] Kreit JW. The impact of right ventricular dysfunction on the prognosis and therapy of normotensive patients with pulmonary embolism. Chest 2004;125:1539–45.

[8] Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mmHg or higher. Arch Intern Med 2005;165:1777–81.

[9] Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J 1997;134:479–87.

[10] Sanchez O, Trinquart L, Colombet I, Durieux P, Huisman MV, Chatellier G, Meyer G. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. Eur Heart J 2008;29:1569–77.

[11] Goldhaber SZ. Echocardiography in the management of pulmonary embolism. Ann Intern Med 2002;136:691–700.

[12] Sato Y, Nishi K, Taniguchi R, Miyamoto T, Fukuhara R, Yamane K, Saijyo S, Tanada Y, Yamamoto E, Goto T, Takahashi N, Fujiwara H, Takatsu Y. In patients with heart failure and non-ischemic heart disease, cardiac troponin T is a reliable predictor of long-term echocardiographic changes and adverse cardiac events. J Cardiol 2009;54:221–30.

[13] Nishikimi T, Kuwahara K, Nakao K. Current biochemistry, molecular biology, and clinical relevance of natriuretic peptides. J Cardiol 2011;57:131–40.

[14] Kline JA, Hernandez-Nino J, Rose GA, Norton HJ, Camargo Jr CA. Surrogate markers for adverse outcomes in normotensive patients with pulmonary embolism. Crit Care Med 2006;34:2773–80.

[15] Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation 2003;108:2191–4.

[16] Mikulewicz M, Lewczuk J. Importance of cardiac biomarkers in risk stratification in acute pulmonary embolism. Cardiol J 2008;15:17–20.

[17] ten Wolde M, Tulevski II, Mulder JW, Sohne M, Boomsma F, Mulder BJ, Buller HR. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. Circulation 2003;107:2082–4.

[18] Tulevski II, ten Wolde M, van Veldhuisen DJ, Mulder JW, van der Wall EE, Buller HR, Mulder BJ. Combined utility of brain natriuretic peptide and cardiac troponin T may improve rapid triage and risk stratification in normotensive patients with pulmonary embolism. Int J Cardiol 2007;116:161–6.

[19] Krüger S, Graf J, Merx MW, Koch KC, Kunz D, Hanrath P, Janssens U. Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. Am Heart J 2004;147:60–5.

[20] Logeart D, Lecuyer L, Thabut G, Tabet JY, Tartiere JM, Chavelas C, Bonnin F, Stievenart JL, Solal AC. Biomarker-based strategy for screening right ventricular dysfunction in patients with non-massive pulmonary embolism. Intensive Care Med 2007;33:286–92.

[21] Meyer T, Binder L, Hruska N, Luthe H, Buchwald AB. Cardiac troponin I elevation in acute pulmonary embolism is associated with right ventricular dysfunction. J Am Coll Cardiol 2000;36:1632–6.

[22] Yardan T, Altintop L, Baydin A, Yilmaz O, Guven H. B-type natriuretic peptide as an indicator of right ventricular dysfunction in acute pulmonary embolism. Int J Clin Pract 2008;62:1177–82.

[23] Pieralli F, Olivotto I, Vanni S, Conti A, Camaiti A, Targioni G, Grifoni S, Berni G. Usefulness of bedside testing for brain natriuretic peptide to identify right ventricular dysfunction and outcome in normotensive patients with acute pulmonary embolism. Am J Cardiol 2006;97:1386–90.

[24] Lega JC, Lacasse Y, Lakhal L, Provencher S. Natriuretic peptides and troponins in pulmonary embolism: a meta-analysis. Thorax 2009;64:869–75.

[25] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of

Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
[26] Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jäckle S, Binder L. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002;106:1263–7.
[27] Amorim S, Dias P, Rodrigues RA, Araújo V, Macedo F, Maciel MJ, Gonçalves FR. Troponin I as a marker of right ventricular dysfunction and severity of pulmonary embolism. Rev Port Cardiol 2006;25:181–6.
[28] Margato R, Carvalho S, Ribeiro H, Mateus P, Fontes P, Moreira JI. Cardiac troponin I levels in acute pulmonary embolism. Rev Port Cardiol 2009;28:1213–22.
[29] Januzzi Jr JL, Bamberg F, Lee H, Truong QA, Nichols JH, Karakas M, Mohammed AA, Schlett CL, Nagurney JT, Hoffmann U, Koenig W. High-sensitivity troponin T concentrations in acute chest pain patients evaluated with cardiac computed tomography. Circulation 2010;121:1227–34.
[30] Sato Y, Yamamoto E, Sawa T, Toda K, Hara T, Iwasaki T, Fujiwara H, Takatsu Y. High-sensitivity cardiac troponin T in essential hypertension. J Cardiol 2011;58:226–31.
[31] Kusumoto A, Miyata M, Kubozono T, Ikeda Y, Shinsato T, Kuwahata S, Fujita S, Takasaki K, Yuasa T, Hamasaki S, Tei C. Highly sensitive cardiac troponin T in heart failure: comparison with echocardiographic parameters and natriuretic peptides. J Cardiol 2012;59:202–8.
[32] Lagrand WK, Visser CA, Hermens WT, Niessen HW, Verheugt FW, Wolbink GJ, Hack CE. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 1999;100:96–102.
[33] Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557–65.
[34] Abul Y, Karakurt S, Ozben B, Toprak A. C-reactive protein in acute pulmonary embolism. J Investig Med 2011;59:8–14.
[35] Adams 3rd JE, Siegel BA, Goldstein JA, Jaffe AS. Elevations of CK-MB following pulmonary embolism. A manifestation of occult right ventricular infarction. Chest 1992;101:1203–6.
[36] Stein PD, Janjua M, Matta F, Pathak PK, Jaweesh F, Alrifai A, Chughtai HL, Stein PD, Janjua M, Matta F, Pathak PK, Jaweesh F, Alrifai A, Chughtai HL. Prognosis based on creatine kinase isoenzyme MB, cardiac troponin I, and right ventricular size in stable patients with acute pulmonary embolism. Am J Cardiol 2011;107:774–7.